REMARKS

Claims 35-40 are pending in this application.

Claim Rejections

Rejection under 35 U.S.C. § 112, first paragraph:

Enablement

The Office action maintains rejection of claims 35-40 for alleged lack of enablement. In particular, the Office action rejects Applicants' reliance on other, similar applications assigned to Genentech in part because "it is noted that the prosecution history of US Patent 7,220,835, for instance, differs from the instant application's history, in that a Declaration that 'provides support for the assertion that the claimed protein decreases the response of the MLR demonstrating immunosuppression in vitro,' was submitted leading to the withdrawal of a rejection made under 35 USC 112 p1, enablement." Page 2-3 of the Office action mailed 4/3/08.

Applicants respectfully request this rejection be withdrawn. On April 3, 2008, Applicants submitted a declaration by the inventors that further demonstrates that claims 27-41 are enabled. A copy of this declaration also is attached hereto for the Examiner's convenience at Tab A. Similar to the declaration the inventors provided in US Patent 7,220,835, in the attached declaration the inventors provide the basic protocol for the MLR assay as well as copies of pages from an internal database showing the positive results for the PRO361 polypeptide in the MLR assay. The assay data shown in Exhibit A to the attached Declaration demonstrates that the PRO361 polypeptide inhibits T-cell proliferation in the MLR assay and provides further evidence that one of ordinary skill in the art would have been able to make and use the claimed nucleic acids for the intended purpose (immune suppression) without undue experimentation.

Indeed, the data submitted with the attached Declaration provides support for Applicants' assertion that the claimed PRO361 decreases the response of the MLR, and thereby demonstrates immunosuppression in vitro. The Office reached this very conclusion based

on the similar declaration submitted during prosecution of US Patent 7,220,835, stating that the declaration and data submitted therewith "provides support for the assertion that PRO1114 (the protein of SEQ ID NO:352) decreases the response of the MLR, demonstrating immunosuppression *in vitro*." (Tab B).

Applicants respectfully submit that this Declaration overcomes the conclusion in the Office action that "there is not sufficient guidance for the actual therapeutic use of the claimed nucleic acid or the polypeptide it encodes." Page 3 of the Office action mailed 4/3/08. For example, following submission of the declaration in US Patent 7,220,835, the Office provided the following "Reasons for Allowance":

> Applicant continues to assert and argue that the instant specification enables use of the claimed invention for suppression of the graft versus host response. This asserted use is not disclosed in the instant specification. However, based on the MLR assay, the data provided in the Declaration filed 25 September 2006, and the teaching in the art that the MLR assay is an art accepted assay for identifying immune suppressive molecules, one of ordinary skill in the art would recognize a well-established use for the claimed invention for at least *in vitro* suppression. Since the claims are not directed to *in vivo* methods of use, this issue need not be further addressed.

(Tab B).

Applicants also respectfully submit that this Declaration overcomes the position in the Office action that the cited portions of the references by Campo, Picotti, and Kahan remain relevant and "provide support for the argument that the claims are not fully enabled since the MLR assay is only generally predictive, but the extensive further research would be required to practice and use the invention claimed." Page 4 of the Office action mailed 4/3/08. The data submitted with this declaration supports Applicants' assertion that the claimed PRO361 decreases the response of the MLR, and thereby demonstrates immunosuppression in vitro. As discussed above, since the claims are not directed to *in vivo* methods of use, the Declaration overcomes the Office's reliance on the cited references.

Importantly, "to comply with 35 U.S.C. 112, first paragraph, it is not necessary to 'enable one of ordinary skill in the art to make and use a perfected, commercially viable

embodiment absent a claim limitation to that effect.' *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003)." MPEP § 2164. Here the claims do not require a commercially viable invention. Rather the claims are simply to an isolated nucleic acid. The claims are supported by a utility based on the MLR assay. According to the MPEP, "[i]f a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). *See also In re Brana*, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993)." MPEP §2164.01(c). As the Office acknowledged during prosecution of US Patent 7,220,835, based on the evidence submitted in this case, one of ordinary skill in the art would recognize a well-established use for the claimed invention for at least *in vitro* suppression.

Additionally, Applicants respectfully submit that 35 U.S.C. § 112 is satisfied here because the art recognizes that standard modes of administration of immunosuppressor compounds are known and contemplated. Indeed, the use of immunosuppressive molecules in the treatment of immunodisorders, such as graft versus host disease, is well known in the art as indicated by various art references including Kahan et al., Picotti et al. and Campo et al., made of record by the Office action, and Fung-Leung et al., Shim et al., and U.S. Patent Nos. 5,817,306, 5,648,376, 5,801,193, and 5,958,403 (all made of record in Applicants' filings of 9/2/2005 and 11/8/2006). Thus, any further experimentation required to determine, for example, the particular dosage or method of administration of PRO361 would not be considered undue. Indeed, there is no requirement to determine exact dosages in order to demonstrate efficacy. Moreover, the applicant need not demonstrate that the invention is completely safe. MPEP § 2164.01(c).

Important here, the MPEP states that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation

and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)." MPEP 2164.01(c). As the Office acknowledges, clearly the art teaches the *in vitro* results of the MLR assay correlate with the *in vivo* results of immunosuppression. For example, as previously noted, U.S. Patent No. 5,817,306 states, "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules in vitro that are useful for treating graft versus host disease. The results obtained from these assays are generally predictive of their in vivo effectiveness" (Column 12, lines 36-41; emphasis added). U.S. Patent No. 5,801,193, filed April 15, 1997, states that "[t]he MLR is an assay recognized by those skilled in the art as an in vitro predictor of in vivo immunosuppressant activity." (Column 8, lines 8-10, emphasis added). U.S. Patent No. 5,648,376, filed January 19, 1995, states that "[a] measure of immunosuppressive that serves as a model for transplantation rejection is inhibition of cell proliferation in a mixed lymphocyte reaction (MLR) assay." (Column 11, lines 24-26).

Hence, Applicants respectfully submit that the Office action has not shown that a lack of correlation between results of the MLR assay in vitro and immunomodulatory activity in vivo is typical. In fact, Picotti et al. and Campo et al., relied on by the Office, support Applicants' position that the in vitro MLR assay can be successfully used to identify compounds having immuno-modulatory activity, particularly immunoinhibitory activity, in vivo. For example, Picotti et al. showed that the IL-12RS1 subunit was critical for IL-12 driven enhanced alloimmune response in vitro and in vivo (see abstract). Campo et al. teach that "the human mixed lymphocyte culture (MLC) is an important method to test donor-recipient compatibility in bone marrow transplantation. It could be shown that cytokine release, especially IFN-, has a very good predictive value with regard to the transplantation outcome, as cytokines play a major role in the generation of an alloreactive immune response and for the induction of graft rejection in vivo..... Landolfo et al. inhibited T-cell reactivity by the addition of anti-IFN- both in vitro and in vivo" (see page 18; emphasis added). Additionally, Applicants' position is further supported by other art references, such as Fung-Leung (previously made of record), which demonstrate that

inhibitors of the MLR find utility in suppressing unwanted immune response, and thus suppress unwanted graft rejection.

Applicants respectfully note that enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." It is well established in the art that a positive result as an inhibitor in the in vitro MLR assay is reasonably correlated to use as a therapeutic compound for the treatment of conditions such as graft vs. host disease. See, for example, Fung-Leung et al., and U.S. Patent No. 5,817,306, filed June 7, 1995, U.S. Patent No. 5,648,376, filed January 19, 1995, and U.S. Patent No. 5,958,403, filed July 11, 1994 (all made of record in Applicants filing of November 8, 2006). The Office action has acknowledged as much by stating that "the MLR assay is an art accepted assay for identifying immune suppressive molecules and the **assay is generally predictive of their in-vivo effectiveness**." Page 2 of the Office Action mailed 9-19-07; emphasis added. Thus, by providing Example 34, which demonstrates that PRO361 tested positive as an inhibitor in the MLR assay, the instant specification has provided all that is required to demonstrate enablement for the claimed PRO361 polypeptides. Moreover, enablement is further demonstrated here by the attached Declaration, which provides data supporting Applicants' assertion that the claimed PRO361 polypeptides decrease the response of the MLR assay, and thereby demonstrate immunosuppression in vitro.

In conclusion, the use of the MLR assay is well established for the identification of immunomodulatory compounds, including compounds that inhibit and compound that stimulate the immune response. Accordingly, based upon the disclosure of the present application and the general knowledge in the art that was available at the time the present invention was made, one of ordinary skill in the art would have been able to use the claimed polypeptides for the intended purpose (immune suppression) without undue experimentation. Therefore, Applicants respectfully request that the enablement rejection of Claims 35-40 under 35 U.S.C. § 112, first paragraph, be withdrawn.

CONCLUSION

Applicants believe this Request for Reconsideration fully responds to the Office action mailed April 3, 2008. Applicants respectfully request the Examiner grant allowance of pending claims 35-40. The Examiner is invited to contact the undersigned attorney for the Applicant via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

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